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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,791	01/08/2005	Alexander Domling	62660(52171)	3248

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EXAMINER	
GUDIBANDE, SATYANARAYAN R	

ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
10/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,791	DOMLING ET AL.	
	Examiner	Art Unit	
	Satyanarayana R. Gudibande	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 12-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of species as compound recited in claim 14 and 17, and addition of claims 14-17 in the reply filed on December 2, 2005 was acknowledged in the non-final office action dated 1/23/06.

Applicant's remarks and amendment to claims in the response filed on 8/6/07 has been acknowledged.

Claims 7-10 and 12-22 are pending.

Claims 7-10 and 12-22 are examined on the merit.

Any objections and rejections made in the previous office action dated 2/5/07 and not specifically mentioned here are considered withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7-10, 14, 15 and 20-22 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sasse, et al., The Journal of Antibiotics, 2000, 53,879-885, in view of Greenwald, Journal of Controlled Release, 2001, 74, 159-171 as stated for claims 7-10 and 12-17 in the office action dated 1/23/06.

Applicants state that they have prepared further experimental data and presented them in the declaration under 37 CFR 1.132. Applicants state that the results presented in the current declaration combined with the earlier declaration filed on November 30, 2006 reveal that coupling of tubulysin with PEG ester, amide or phenol reduces the activity of the respective compounds in two cancer lines thus leading to tubulysin derivatives of lower activity commensurate with the object of the invention indicated in the specification in paragraph [0004].

Applicants further argue that the cited reference of Greenwald teaches two types of PEG-drug conjugates, permanently bonded and non-permanently bonded PEG drug conjugates and state that permanently bonded PEG-drugs comprise PEG linkers of mol. Wt. 2000-5000 and the declaration field on November 30, 2006 indicate that the PEG-derivatives having PEG linker

with high molecular weight such as 35-40 kDa provide better results with regards to the object of the invention than low molecular weight PEG's. Applicants argue that this aspect of Greenwald teaching teaches away from the teachings of the present invention.

Applicants further argue that the section 3 of the Greenwald teaches pro-drugs that require an enzymatic transformation within the body in order to release the active drug and has improved delivery properties over the parent molecule. Applicants argue that this scenario does not apply to the tubulysin derivatives, because as stated in the paragraph [0003], tubulysin possesses a high toxicity and if derivatives released free tubulysin immediately after absorption, the free tubulysin exert their cytotoxic effect resulting in extensive cell death in normal cells. Applicants state that the object of the instant invention is to enhance the selectivity of tubulysin.

Applicants state that the tubulysin derivatives according to claim 7 are stable in plasma/buffer and less toxic than natural tubulysin as indicated with the declaration dated November 30, 2006 and the instantly enclosed declaration. Applicants further state that they found surprisingly that tubulysin derivatives have entered cancer cells, free tubulysin is released and exert high cytotoxic activity in the cancer cells and these finding are by no means obvious by the publication of Sasse in combination with Greenwald.

Applicants further argue that "[t]he poster attached to the enclosed Declaration, tubulysin derivatives additionally comprising a cyclodextrin group solve the object of the present invention. In fact, cyclodextrin-PEG-polymer conjugates of tubulysin show high antiproliferative activity in human cancer cells (cf, table 1), but are significantly less toxic than tubulysin A (cf. table 2). As evident from table 3 and graph 1, cyclodextrin conjugates of tubulysin are better tolerated than vinblastine and tubulysin A and lead to a significant increase in tumor growth

delay, inhibit the formation of new tumor cells and at the same time reduce the number of existing tumor cells. It is again pointed out that the Sasse publication does not pertain to tubulysin conjugates and that the Greenwald publication does not disclose cyclodextrin conjugates at all. As a consequence, the claimed invention is by no means rendered obvious by the publications of Sasse in and Greenwald".

Applicant's arguments filed 8/6/07 have been fully considered but they are not persuasive, because, applicants argument that the combination of results in the two declarations presented under 37 CFR 1.132 indicates that activity of the tubulysin conjugated to PEG can be dramatically reduced thus leading to tubulysins with lower toxicity has been illustrated in Greenwald reference, "usually the specific activity of protein declines after modification (pegylation)" (column 2, page 159, paragraph 1). Thus the fact the specific activity of a particular compound decreases upon pegylation is well known in the literature.

Applicant's argument that Greenwald teaches permanently bonded PEG-drugs that comprises of molecular weight 2-5kDa and the instant invention teaches PEG-derivatives of 35-40 kDa and provide better result with regards to object of the instant invention is not persuasive, because, the cited reference of Greenwald does teach PEG conjugates of drugs with >20kDa and especially 40kDa has been shown (section 3.2, page 161, column 1 and 2) wherein conjugates of 5 to 40 kDa PEG conjugates have been illustrated. Applicant's argument that the conjugation of tubulysin to PEG of molecular weight 35-40 kDa leads to better results have been addressed in the previous office action dated 2/5/07. It is reiterated here that applicants have shown in their Rule 132 declaration dated 11/30/06, that the pegylation of tubulysin enhanced the solubility by

10-40 fold in phosphate buffer, however, the cited prior art of Greenwald shows that the solubility of anticancer drug campothecin (CPT) increased to 2 mg/ml from 0.0025 mg/mL which is -800 fold. Therefore, the result obtained by applicants is not unexpected over the prior art.

Applicant's argument that section 3 of the Greenwald teaches PEG pro-drugs and the instant invention is not a prodrug derivative is irrelevant. Applicants invention is drawn to PEG conjugates of tubulysin and the reference of Greenwald teaches many different conjugates of drugs with PEG and some of them are in the prodrug form. The important fact to remember here is that the cited reference teaches the conjugates of PEG that is the focus of the instant invention and not the functional aspect of the conjugates.

Applicant's statement that they surprisingly found that the tubulysin derivatives are stable in plasma/buffer and less toxic than natural tubulysins according to the data provided in the two declarations dated 11/30/06 and 8/6/07 are not persuasive, because, these facts are well known in the prior art. The cited reference of Greenwald clearly states that the PEG modification extends the half-life of the drug in plasma and lowers the specific activity of the drug upon pegylation (page 159, column 2).

Applicants further stated that the cyclodextrin-PEG-polymer conjugates of tubulysin derivatives show high antiproliferative activity in human cells and are less toxic than tubulysin A. The instant invention is drawn to PEG-conjugates of tubulysin and not cyclodextrin conjugates of tubulysin (the elected species is a PEG conjugate of tubulysin), and hence, the result obtained with an unrelated conjugate of the drug becomes irrelevant in this instant case. Moreover, the figure in the poster presented as evidence is of poor quality to obtain any useful

information. Applicants have again point out that Sasse publication does not pertain to tubulysin conjugates and Greenwald publication does not disclose cyclodextrin conjugates, this is not persuasive, because, if Sasse disclosed tubulysin conjugates, the rejection would have been made under anticipation statute and not under obviousness statute. Moreover, as mentioned earlier the instant invention pertains to PEG conjugates and not cyclodextrin conjugates.

Therefore, the rejection under obviousness over Sasse in view of Greenwald is proper and is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12, 13, 16-19 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement as stated for claims 7-10 and 12-17 in the office action dated 1/23/06.

Applicant should submit an argument under the heading "Remarks" pointing out disagreements with the examiner's contentions. Applicant must also discuss the references applied against the claims, explaining how the claims avoid the references or distinguish from them. In the absence of arguments, the claim amendments made in the response filed on 8/6/07 is insufficient to overcome the 112 first paragraph rejection failing to comply with the enablement requirement.

Claims 1-10 and 12-22 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention as stated in the office action dated 2/5/07.

Applicant should submit an argument under the heading "Remarks" pointing out disagreements with the examiner's contentions. Applicant must also discuss the references applied against the claims, explaining how the claims avoid the references or distinguish from them. In the absence of arguments, the claim amendments made in the response filed on 8/6/07 is insufficient to overcome the 112 first paragraph rejection failing to comply with the written description requirement.

New grounds of rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recite a limitation "R^{13}" as a variable. The currently amended claim does not have a variable "R^{13}" in the formula (I). Therefore, the presence of the variable "R^{13}" renders the claim vague and indefinite.

Applicant's amendment to claim 7, necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Satyanarayana R. Gudibande, Ph.D.
Art Unit 1654

10/21/08
ANISH GUPTA
PRIMARY EXAMINER